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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/838,286	04/20/2001	Jacques Dumas	BAYER-14	9096

23599 7590 06/28/2006

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EXAMINER	
KWON, BRIAN YONG S	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 06/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/838,286	DUMAS ET AL.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26 and 39-74* is/are pending in the application.

4a) Of the above claim(s) *26,39-49,51 and 57-74* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50 and 52-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. In view of the Appeal's Brief filed on May 03, 2006, PROSECUTION IS HEREBY REOPENED. New ground of rejection is set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below: Ardin H. Marschel 6/22/06

ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER

Response to Arguments

2. Applicant's arguments with respect to claims 50 and 52-55 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 50 and 52-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating the specific disease mediated by p38 (i.e., rheumatoid arthritis, osteoarthritis and septic arthritis) by the specific compounds of the formula I (e.g., 4-ter-Butyl-2-pyridyl ureas), does not reasonably provide enablement for "a method of treating a disease mediated by p38 within a host", "the treatment of a disease other than cancer" with "a compound of Formula I ". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The claimed invention is directed to a method for the therapeutic treatment of all types of diseases mediated by p38 including cancer (claims 50, 52-54) or all types of diseases mediated by p38 other than cancer (claim 55), comprising administering said compounds represented by the Formula I.

The nature of the invention is extremely complex in that it encompasses anticipating multiple complex disorders having unrelated manifestations and subsequently administering the instantly claimed plethora of compound(s) represented by the formula.

The specification discloses that because inhibition of p38 leads to inhibition of cytokines (e.g., Tiff production, IL-1 and IL-8) and inhibition of proteolysis enzymes (e.g., MMP-1 and MMP-3) production, p38 inhibitors are useful in the treatment of the diseases or condition encompassed by the instant claims including arthritis, rheumatic fever, bone resumption, postmenopausal osteoporosis, sepsis, gram negative sepsis, septic shock, end toxic shock, toxic shock syndrome, systemic inflammatory response syndrome, inflammatory bowel diseases including Cohn's disease and ulcerative colitis, Jarisch-Herxheimer reactions, asthma, adult respiratory distress syndrome, acute pulmonary fibrotic disease, Pulmonary sarcoidosis, allergic respiratory diseases, silicosis, coal worker's pneumoconiosis, alveolar injury, hepatic failure, liver disease during acute inflammation, severe alcoholic hepatitis, malaria including Plasmodium falciparum malaria and cerebral malaria, non-insulin-dependent diabetes mellitus DM), congestive heart failure, damage following heart disease, atherosclerosis, Alzheimer's disease, acute encephalitis, brain injury, multiple sclerosis including demyelation and oligodendrocyte loss in multiple sclerosis, advanced cancer, lymphoid malignancies, tumor metastasis, pancreatitis including systemic complications in acute pancreatitis, impaired wound

healing infection, inflammation and cancer, periodontal diseases, corneal ulceration, proteinuria,myelodysplastic syndromes, systemic lupus erythematosus, biliary cirrhosis, bowel necrosis, psoriasis, radiation injury, toxicity following administration of monoclonal antibodies such as OKT3, host-versus-graft reactions including ischemia reperfusion injury and allograft rejections including kidney, liver, heart, and skin allograft rejections, lung allograft rejection including chronic lung allograft rejection (alliterative bronchitis)as well as complications due to total hip replacement, and infectious diseases including tuberculosis, Helicobacter pylori infection during peptic ulcer disease, Chaka's disease resulting from Trypanosome cruse infection, effects of Shiga-like toxin resulting from E. coli infection, effects of enter toxin A resulting from staphylococcus infection, meningococcal infection, and infections from Borealis burgdorferi, Treponema pallidium, cytomegalovirus, influenza virus, Theiler's encephalomyelitis virus, and the human immunodeficiency virus (H1V).
(page 4, lines 30-31; page 5, lines 18-31; page 6, lines 14-26; page 6, line 27 thru page 7, line 23).

With respect to the scope of enablement for the treatment of disease mediated by p38,

There are no known compounds of similar structure which have been demonstrated to treat (i) all types of diseases that are mediated thru p38 or (ii) all types of diseases other than cancer that are mediated thru p38. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of pharmacotherapeutics.

Contrary to the instant invention, the art recognizes that the inhibition of p38 is not useful for the treatment of asthma (Chialda et al., Respiratory Research 2005, 6:36, pp. 1-19) and interstitial lung diseases and pulmonary fibrosis (Kapoun et al., Molecular Pharmacology, abstract, 2006, www.molpharmaspetjournals.org).

Furthermore, the art recognizes that drugs blocking p38 have been hindered by drug toxicity in human (Feldmann, M., Nature Immunology, 2001, Vol. 2, No. 9, pp. 771-773).

In addition, in cancer therapy art, it is recognized that different types of cancers affect different organs and have different method of growth and harm the body. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Also see In re Buting, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against all cancers or cancers mediated by p38.

The relative skill of those in the art of pharmaceuticals and the unpredictability of the art is high. Thus, based on the state of art knowledge, one having ordinary skill in the art would not have expected that the administration of said compounds would be able to treat all of disease condition mediated by p38. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Moreover, one of skill in the art would recognize that it is highly unpredictable in regard to therapeutic effects, side effects, and especially serious toxicity when and/or after administering to a host (e.g., a human) any compound represented by formula I. See "Goodman & Gilman's The Pharmacological Basis of Therapeutics" regarding possible drug-drug interactions (9th ed., 1996), page 51, in particular. Goodman & Gilman teaches that "The frequency of significant beneficial or adverse drug interactions is unknown" (see the bottom of the left column of page 51) and that "Recognition of beneficial effects and recognition of and prevention of adverse drug interaction require a thorough knowledge of the intended and possible effects of drugs that are prescribed" and the "The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences" (see the right of page 51). In the instant case, in the absence of fully recognizing the identify of the member genus herein, one of skill in the art would not be able to fully predict possible adverse drug-drug interactions occurring with many combinations of any compounds having the claimed functional properties in the pharmaceutical compositions herein. Thus, the teachings of Goodman & Gilman (in light of above mentioned Feldmann, M., Nature Immunology, 2001, Vol. 2, No. 9, pp. 771-773) clearly support that the instant claimed invention is highly unpredictable.

As mentioned above, the scope of the instant claims encompasses over 100 different types of diseases that may be related to p38 pathway mechanism. The specification discloses that inhibition of p38 inhibits both cytokine production (eg., TNFα, IL-1, Il-6, IL-8) and proteolytic enzyme production (e.g., MMP-1, MMP-3). See page 2, lines 10-13. The specification correlates to various diseases that are related to excessive levels of TNFα, excess or undesired matrix-

destroying metalloprotease (MMP) activity or an imbalance in the ratio of the MMPs to the tissue inhibitors of metalloproteinases. See page 2, line 14 thru page 5, line 17.

The specification discloses the p38 inhibitory activity of the compounds in vitro assay (bottom of page 74 thru page 75) and the activity of the claimed inhibitors of p38 in murine lipopolysaccharide (LPS) model (in vivo) of TNFα production (page 75). However, the guidance given by the specification as to what types of ureas would be useful in a method of the instant invention is limited.

As stated above, the specification does not provide any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds for the treatment of all of the claimed disease conditions that are mediated by p38. As a result, one of skill in the art would be forced to perform an exhaustive search for the embodiments of any drugs having the function recited in the instant claim suitable to practice the claimed invention. Furthermore, one of skill in the art would have to determine not only which compounds inhibit p38, but which compounds actually treat all of diseases mediated by p38 mechanism without undue amount of experimentation.

Since the efficacy of the claimed compounds in treating all of complex diseases condition may have unrelated manifestation mentioned above cannot be predicted from a priori but must be determined from the case to case by painstaking experimental study and when the above factors are weighed together, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to use the invention commensurate in scope with the claims.

With respect to the scope of enablement for "compound for Formula I",

There are no known compounds of similar structure which have been demonstrated to treat (i) all types of diseases that are mediated thru p38 or (ii) all types of diseases other than cancer that are mediated thru p38. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of pharmacotherapeutics.

Contrary to the instant invention, it is known that the modification of urea core group with different substituents would have different physiological activity. For example, deletion of the two chlorine atoms or replacement of the chlorine atoms by methyl group in substituted phenyl ring attached to urea results in inactive compounds or weaker compound (Dumas et al., Bioorganic & Medicinal Chemistry Letters, 10, 2000, 2047-2050).

Furthermore, the art recognizes that drugs blocking p38 have been hindered by drug toxicity in human (Feldmann, M., Nature Immunology, 2001, Vol. 2, No. 9, pp. 771-773).

The relative skill of those in the art of pharmaceuticals and the unpredictability of the pharmaceutical art is very high. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970). Thus, one having ordinary skill in the art would not have predicted that all of the compounds represented by the instant formula would provide the claimed therapeutic utility without undue amount of experimentation.

The breadth of the claims encompasses plethora of compound(s) represented by the formula (over thousands compounds).

The instant specification discloses the preparation or synthesis of the instant compounds represented by the Formula I by known chemical reactions and procedures (page 18, line 3 thru page 22, line 2; page 29, line 3 thru page 74, line 3). Furthermore, the specification discloses the p38 inhibitory activity of the compounds in vitro assay (bottom of page 74 thru page 75) and the activity of the claimed inhibitors of p38 in murine lipopolysaccharide (LPS) model (in vivo) of TNFα production (page 75).

Although the specification provide sufficient guidance in how to make compounds that are suitable for the claimed invention, the specification fails to provide sufficient clarity in how to use it. The specification provides no guidance, in the way of enablement for the full scope of all compounds that are potentially suitable for the invention work similarly without known toxicity concern. The skill artisan would have not known that which compounds of the claimed compounds are capable of accomplishing the desired result of the claimed invention **without undue amount of experimentation**.

As discussed above, none of the specification provides enabling disclosure for the full scope of all compounds that would behave similar without known toxicity concern. There is no demonstrated correlation that the tests and results apply to the claimed utility embraced by the instant claims.

Since the efficacy of the claimed compounds in treating all of complex diseases condition by all of compounds encompassed by the instant invention cannot be predicted from a priori but must be determined from the case to case by painstaking experimental study and when the above factors are weighed together, one of ordinary skill in the art would be burdened with

undue "painstaking experimentation study" to use the invention commensurate in scope with the claims.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 50 and 52-56 are rejected under the judicially created doctrine of double patenting over claims 17-24, 26, 30-32 of copending U.S. Application No. 09/776,935

Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the copending application overlaps with the instantly claimed invention.

Both the instant application and the copending applications are directed to the administration of same compounds encompassed by the formula I to potentially same subject matter, for example patient having rheumatoid arthritis or osteoarthritis to treat same conditions. Although the instant invention differs from the copending application by the selection of the specific species from the generic formula, the copending application makes obvious the claimed

invention since the species of the genus or subgenus are taught as having similar properties of the claimed invention.

5. Claims 50 and 52-56 are rejected under the judicially created doctrine of double patenting over claims 1, 3-4 and 7-11 of copending U.S. Application No. 10/086417.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the copending application overlaps with the instantly claimed invention.

Both the instant application and the copending applications are directed to the administration of same compounds encompassed by the formula I to potentially same subject matter, for example patient having rheumatoid arthritis or osteoarthritis to treat same conditions. Although the instant invention differs from the copending application by the selection of the specific species from the generic formula, the copending application makes obvious the claimed invention since the species of the genus or subgenus are taught as having similar properties of the claimed invention.

6. In looking in continuity data, it is noted that applicant has numerous issued patent or pending application encompassing the same or similar subject matter of the instant application. Applicant review all subject matter considered same or similar, and submit the proper Terminal Disclaimer(s). For example, 11/158,048, 10/071,248, 10/060,396 and 10/361,859 to be same or similar subject matter(s).

Conclusion

7. No Claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Brian Kwon
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